Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial

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Summary

Background First-line pembrolizumab monotherapy improves overall and progression-free survival in patients with untreated metastatic non-small-cell lung cancer with a programmed death ligand 1 (PD-L1) tumour proportion score (TPS) of 50% or greater. We investigated overall survival after treatment with pembrolizumab monotherapy in patients with a PD-L1 TPS of 1% or greater.

Methods This randomised, open-label, phase 3 study was done in 213 medical centres in 32 countries. Eligible patients were adults (≥18 years) with previously untreated locally advanced or metastatic non-small-cell lung cancer without a sensitising *EGFR* mutation or *ALK* translocation and with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, life expectancy 3 months or longer, and a PD-L1 TPS of 1% or greater. Randomisation was computer generated, accessed via an interactive voice-response and integrated web-response system, and stratified by region of enrolment (east Asia *vs* rest of world), ECOG performance status score (0 *vs* 1), histology (squamous *vs* non-squamous), and PD-L1 TPS (≥50% *vs* 1–49%). Enrolled patients were randomly assigned 1:1 in blocks of four per stratum to receive pembrolizumab 200 mg every 3 weeks for up to 35 cycles or the investigator's choice of platinum-based chemotherapy for four to six cycles. Primary endpoints were overall survival in patients with a TPS of 50% or greater, 20% or greater, and 1% or greater (one-sided significance thresholds, p=0·0122, p=0·0120, and p=0·0124, respectively) in the intention-to-treat population, assessed sequentially if the previous findings were significant. This study is registered at ClinicalTrials.gov, number NCT02220894.

Findings From Dec 19, 2014, to March 6, 2017, 1274 patients (902 men, 372 women, median age 63 years [IQR 57–69]) with a PD-L1 TPS of 1% or greater were allocated to pembrolizumab (n=637) or chemotherapy (n=637) and included in the intention-to-treat population. 599 (47%) had a TPS of 50% or greater and 818 patients (64%) had a TPS of 20% or greater. As of Feb 26, 2018, median follow-up was 12·8 months. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group in all three TPS populations (≥50% hazard ratio 0·69, 95% CI 0·56–0·85, p=0·0003; ≥20% 0·77, 0·64–0·92, p=0·0020, and ≥1% 0·81, 0·71–0·93, p=0·0018). The median surival values by TPS population were 20·0 months (95% CI 15·4–24·9) for pembrolizumab versus 12·2 months (10·4–14·2) for chemotherapy, 17·7 months (15·3–22·1) versus 13·0 months (11·6–15·3), and 16·7 months (13·9–19·7) versus 12·1 months (11·3–13·3), respectively. Treatment-related adverse events of grade 3 or worse occurred in 113 (18%) of 636 treated patients in the pembrolizumab group and in 252 (41%) of 615 in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively.

Interpretation The benefit-to-risk profile suggests that pembrolizumab monotherapy can be extended as first-line therapy to patients with locally advanced or metastatic non-small-cell lung cancer without sensitising *EGFR* or *ALK* alterations and with low PD-L1 TPS.

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Introduction

The ultimate objective of treating advanced non-small-cell lung cancer is to improve overall survival and quality of life. Before the availability of molecularly targeted therapy, advanced non-small-cell lung cancer was treated with chemotherapy, which is associated with a median survival of approximately 12 months[1] and has a poor adverse event profile. Targeted therapies have become standard first-line therapy for patients with driver oncogenes. Median survival in phase 3 trials ranged from 18·6 months to 30·5 months for tyrosine-kinase inhibitors targeting *EGFR* mutations[2–4] and extends beyond 4 years for those

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on June 15, 2018, with the term "PD-1 OR PD-L1 OR MK-3475 OR pembrolizumab OR Keytruda OR BMS-936558 OR nivolumab OR Opdivo OR MPDL3280A OR atezolizumab OR Tecentriq OR MEDI4736 OR durvalumab OR Imfinzi OR MSB0010718C OR avelumab OR Bavencio AND metastatic AND first line OR previously untreated AND non-small cell lung cancer OR NSCLC." We also used this term to search the abstracts from the 2017 and 2018 American Society of Clinical Oncology annual meetings and the 2016 and 2017 European Society for Medical Oncology congresses to identify results of clinical trials not yet published in full. We applied no other search parameters. We identified several randomised, phase 3 studies of patients with metastatic non-small-cell lung cancer treated with antibodies against programmed death protein 1 (PD-1) or its ligand PD-L1. The KEYNOTE-024 study showed significantly longer progression-free and overall survival with pembrolizumab monotherapy than with platinum-doublet chemotherapy in patients with a PD-L1 tumour proportion score (TPS) of 50% or greater. The CheckMate 026 study did not show improved overall survival with nivolumab monotherapy versus platinum-doublet chemotherapy in the primary population of patients with a PD-L1 expression level of 5% or greater. The KEYNOTE-189 study showed that first-line treatment with pembrolizumab plus platinum-doublet chemotherapy significantly prolonged overall survival and progression-free survival compared with chemotherapy alone, irrespective of PD-L1 TPS, in patients with non-squamous non-small-cell lung cancer. The KEYNOTE-407 study demonstrated similar findings in patients with squamous non-small-cell lung cancer. The IMpower131 study of atezolizumab plus platinum-doublet chemotherapy showed significantly prolonged progression-free survival versus platinum-doublet chemotherapy alone in patients with squamous non-small-cell lung cancer, irrespective of PD-L1 expression. The IMpower150 study showed that the combination of atezolizumab, bevacizumab, and platinum-doublet chemotherapy significantly prolonged progression-free and overall survival in patients with non-squamous non-small-cell lung cancer, irrespective of PD-L1 expression or *EGFR* or *ALK* genetic alteration status. The CheckMate 227 study showed that nivolumab plus ipilimumab significantly prolonged progression-free survival versus platinum-doublet chemotherapy in patients with a high tumour mutational burden, irrespective of PD-L1 expression.

Added value of this study

The randomised phase 3 KEYNOTE-042 trial of pembrolizumab monotherapy versus chemotherapy as first-line treatment enrolled patients with locally advanced or metastatic non-small-cell lung cancer and a PD-L1 TPS of 1% or greater, expanding the population of patients compared with that assessed in the KEYNOTE-024 study. Overall survival was assessed as the primary endpoint, and we found a significant survival benefit in patients with PD-L1-positive tumours. The effect was greatest in patients with a TPS of 50% or greater, but remained significant in patients with a TPS of 1% or greater. Despite longer exposure to pembrolizumab treatment than to chemotherapy, the frequency of treatment-related adverse events, including those of grade 3 or worse, was lower in the pembrolizumab group.

Implications of all the available evidence

With our findings of a survival benefit and manageable safety profile for pembrolizumab monotherapy as first-line treatment in patients with PD-L1-positive, locally advanced or metastatic non-small-cell lung cancer, we suggest that use of this drug can be extended to previously untreated patients with a TPS as low as 1%. In the absence of direct prospective comparisons of pembrolizumab given alone and in combination with chemotherapy, patients with PD-L1-positive non-small-cell lung cancer should discuss the benefits and risks of each regimen with their physicians when choosing first-line therapy.

targeting *ALK* alterations.[5–7] For patients without driver oncogenes, however, improvements in survival were minimal until immunotherapeutic options became available.

Pembrolizumab is a humanised IgG4 monoclonal antibody against programmed cell death protein 1 (PD-1). The phase 1 KEYNOTE-001[8] and phase 2/3 KEYNOTE-010[9] studies established the correlation between increased expression of the PD-1 ligand PD-L1 and benefit from treatment with pembrolizumab in patients with advanced non-small-cell lung cancer. KEYNOTE-024[10,11] was a phase 3 study that compared pembrolizumab monotherapy with platinum-based chemotherapy as first-line treatment in 305 patients with metastatic non-small-cell lung cancer and a PD-L1 tumour proportion score (TPS) of 50% or greater. The primary endpoint of progression-free survival and the key secondary endpoint of overall survival were significantly prolonged in the pembrolizumab group compared with in the standard chemotherapy group (median 10·3 months *vs* 6·0 months and 30·0 months *vs* 14·2 months, respectively).

In the international, randomised, open-label, phase 3 KEYNOTE-042 study, we compared pembrolizumab monotherapy with platinum-based chemotherapy as first-line therapy for patients with locally advanced or metastatic non-small-cell lung cancer and a PD-L1 TPS of 1% or greater. Here we report data from the second interim analysis.

Methods

Study design and patients

This randomised, open-label, phase 3 study was done at 213 sites in Argentina, Brazil, Bulgaria, Canada, Chile, China and Hong Kong Special Administrative Region,

Colombia, Czech Republic, Estonia, Guatemala, Hungary, Japan, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, and Vietnam. Patients were eligible for enrolment if they were aged 18 years or older, had locally advanced or metastatic non-small-cell lung cancer without a sensitising *EGFR* mutation or *ALK* translocation, had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, had received no previous therapy for locally advanced or metastatic disease, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, had life expectancy of 3 months or longer, and had a PD-L1 TPS of 1% or greater. We excluded patients if they had known unstable or untreated central nervous system metastases, had a history of non-infectious pneumonitis that required systemic glucocorticoids, had active autoimmune disease, were receiving systemic immunosuppressive treatment, or had a known active hepatitis B or C virus infection. Full inclusion and exclusion criteria are included in the trial protocol (appendix).

The protocol and all amendments were approved by the appropriate ethics committee at each centre. The trial was done in accordance with the protocol, its amendments, and the standards of Good Clinical Practice. All patients provided written informed consent before enrolment.

Randomisation and masking

The randomisation schedule was generated by a computerised randomised list generator and held centrally. Patients were assigned 1:1 to receive pembrolizumab 200 mg alone or the investigator's choice of carboplatin to achieve an area under the curve of 5–6 mg/mL per min plus paclitaxel 200 mg/m² or pemetrexed 500 mg/m². Treatment assignments were obtained via an interactive voice-response and integrated web-response system (Almac Clinical Technologies, Souderton, PA, USA). All drugs were administered intravenously every 3 weeks. Randomisation was stratified by region of enrolment (east Asia *vs* rest of world), ECOG performance status score (0 *vs* 1), histology (squamous *vs* non-squamous), and PD-L1 TPS (≥50% *vs* 1–49%), and treatment was allocated in blocks of four in each stratum.

Treatment was open label because the differences in infusion durations, administration schedules, and requirements for premedication would have made masking difficult. Thus, patients, investigators, members of the external data monitoring committee, and select representatives of the sponsor were not masked, but the central radiological reviewers were unaware of treatment assignment.

Procedures

Treatment was continued until radiographic progression, the patient developed intolerable toxic effects, the investigator decided to stop treatment, or the patient withdrew consent, up to a maximum of 35 cycles in the pembrolizumab group and for four to six cycles in the chemotherapy group. Maintenance therapy with pemetrexed 500 mg/m² every 3 weeks was optional but was encouraged in patients with non-squamous histology who were allocated to the chemotherapy group. Patients with radiographic disease progression who were clinically stable could continue study treatment until progression was confirmed on a scan obtained at least 4 weeks later. No crossover from the chemotherapy group to pembrolizumab was allowed as part of the study.

PD-L1 expression was assessed during screening at two central laboratories (one for China and one for the rest of the world) with the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) and measured in formalin-fixed tumour samples obtained by core-needle or excisional biopsy of a tumour lesion or from tissue resected at or after the time metastatic disease was diagnosed. Expression was categorised by TPS, which was defined as the percentage of tumour cells with membranous PD-L1 staining.[12] TPS results were not revealed to the sponsor, investigator, or site staff. Radiographic tumour imaging was done at baseline and scheduled for every 9 weeks for the first 45 weeks, then every 12 weeks thereafter. Response was assessed according to RECIST version 1.1 by masked and independent central review.

Adverse events were reported during study treatment and for 30 days after treatment ended. Serious adverse events and events of special interest in relation to pembrolizumab treatment were reported for 90 days after treatment ended. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. During follow-up, patients were contacted every 2 months to assess survival.

Outcomes

In the original protocol, written in 2014, the primary endpoint was overall survival in patients with a PD-L1 TPS of 50% or greater and secondary endpoints were overall survival in patients with a PD-L1 TPS of 1% or greater and progression-free survival in patients with a TPS of 50% or greater and of 1% or greater. Exploratory endpoints were overall and progression-free survival in patients with a TPS of 1–49% and objective response among those with a TPS of 50% or greater, 1–49%, and 1% or greater. In 2015, after the enrolment of 662 patients, a significant overall survival benefit was reported in patients with previously treated advanced non-small-cell lung cancer and a PD-L1 TPS of 1% or greater in the KEYNOTE-010 study of pembrolizumab versus docetaxel.[9] Consequently, the primary endpoints in our study protocol were amended to overall survival in patients with a PD-L1 TPS of 50% or greater and of 1% or greater, and the secondary and exploratory endpoints were amended to include progression-free survival and objective response, respectively, in these populations. In

April 2017, after enrolment was complete, we introduced an intermediate TPS cutoff point. This decision was based on an analysis of data from KEYNOTE-010[9] and the results of the CheckMate 026 study[13] of nivolumab versus chemotherapy in patients with previously untreated metastatic non-small-cell lung cancer and a PD-L1 expression level of 1% or greater. We changed the primary endpoints to overall survival in patients with a PD-L1 TPS of 50% or greater, 20% or greater, and 1% or greater and secondary endpoints to progression-free survival and objective response in these populations. All endpoint changes were complete before data lock. Safety, a secondary endpoint since the original protocol, was assessed by clinical review of adverse events, laboratory tests, and vital signs in the overall study population (ie, PD-L1 TPS ≥1%). Duration of response was a protocol-specified exploratory endpoint.

Overall survival was defined as the time from randomisation to death from any cause. Progression-free survival was defined as the time from randomisation to radiologically confirmed disease progression or death from any cause. Objective response was defined as the proportion of patients with radiologically confirmed complete or partial response. Duration of response was defined as the time from first documented complete or partial response to radiologically confirmed disease progression or death from any cause. Response and disease progression were assessed by masked independent central review according to RECIST version 1.1.

Statistical analysis

Overall survival, progression-free survival, and objective response were assessed in the intention-to-treat population, defined as all patients alive at the time of random allocation to a treatment group. Duration of response was assessed in all patients who had complete or partial response. Safety was assessed in the as-treated population, defined as all randomly allocated patients who received at least one dose of study treatment.

SAS version 9.4 was used for all statistical analyses. The Kaplan-Meier method was used to estimate overall survival, progression-free survival, and duration of response. Data for patients who were alive or lost to follow-up were censored at the time of last contact for estimation of overall survival. Data for patients without disease progression or who were lost to follow-up were censored at the time of last tumour imaging for estimation of progression-free survival. Data for patients who were alive without evidence of disease progression but who discontinued the study without radiographical evidence of progression were censored at the time of the last radiographical assessment showing response. For progression-free survival and duration of response, data for patients who started new anticancer therapy without radiographic evidence of progression were censored at the time of the last tumour assessment before new anticancer therapy was initiated.

The stratified log-rank test was used to assess between-group differences in overall and progression-free survival. A stratified Cox regression model with Efron's method of tie handling[14] was used to estimate hazard ratios (HRs) and associated 95% CIs. The stratified Miettinen and Nurminen method[15] was used to assess between-group differences in response rate. All randomisation stratification factors were applied to all stratified analyses.

The evolution of the statistical analysis plan and study endpoints related to protocol amendments is summarised in the appendix. The final protocol specified two interim analyses and a final analysis. The hypotheses of overall survival and progression-free survival were assessed sequentially by TPS, in the order of 50% or greater, 20% or greater, and 1% or greater. Hypotheses were tested only if superiority was established for the preceding hypothesis. The family-wise type I error was strictly controlled at a one-sided α of 0·025. Accounting for the 0·01576 α spent at the first interim analysis, the superiority boundaries were adjusted for multiplicity with the Hwang-Shih-DeCani α spending function,[16] with the γ parameter set at –0·9023 and an information fraction of 1166 of 1353 (ie, the numbers of study days to the second interim analysis and the planned final analysis, respectively, from the date the first patient was randomised). Assuming overall survival follows an exponential distribution with a median of 13 months,[17] an HR for overall survival of 0·65 between the pembrolizumab and chemotherapy groups among patients with a TPS of 50% or greater, an enrolment period of approximately 26 months, a minimum follow-up period of 19 months after completion of enrolment, and a dropout rate of 0·003 per month for overall survival, we calculated that a sample size of approximately 1240 patients would provide the power at the following levels with a one-sided α of 0·025: 99% to detect an HR of 0·65 among patients with a TPS of 50% or greater with 398 deaths in the population; 98% to detect piecewise HRs of 0·80 from 0 to 6 months of treatment and 0·64 after 6 months of treatment among patients with a TPS score of 20% or greater with 557 deaths; and 91% to detect piecewise HRs of 0·92 for 0 to 6 months of treatment and 0·73 after 6 months of treatment among patients with a TPS of 1% or greater with 900 deaths. We used piecewise HRs to account for the possibility of non-proportional hazards in the treatment effect of pembrolizumab versus chemotherapy.

The first interim analysis was planned for around 6 months after the final patient was enrolled and was done using a data cutoff of Aug 30, 2017. After reviewing results, the external data monitoring committee recommended that the study continue as planned. The second interim analysis was based on a cutoff date of Feb 26, 2018, and was done 38·3 months after enrolment of the first patient. The multiplicity-adjusted significance thresholds are summarised in the appendix. The external monitoring committee reviewed the results on April 6, 2018, and

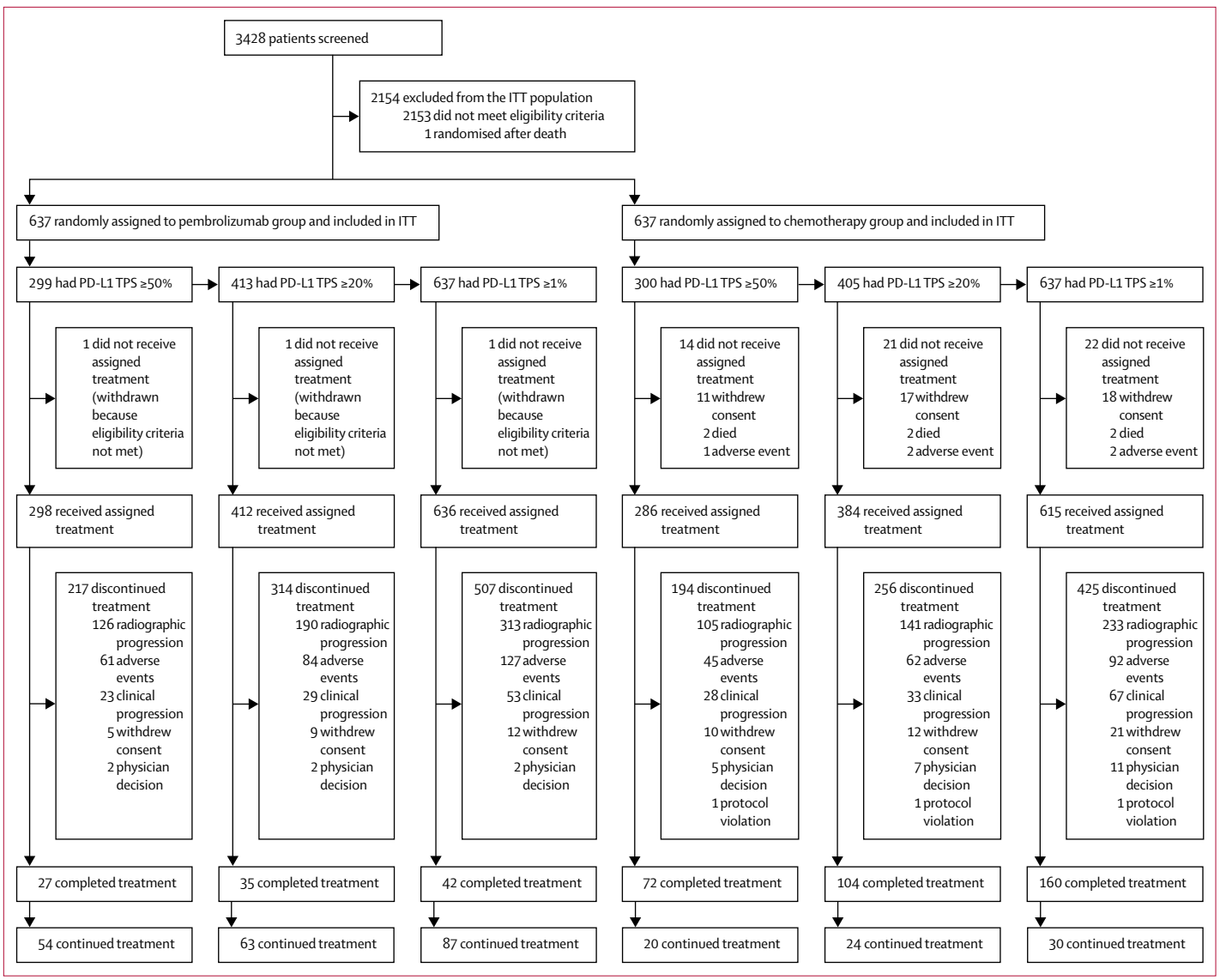

Figure 1: **Trial profile**
The PD-L1 TPS populations were analysed sequentially, from ≥50% to ≥20% to ≥1%. ITT=intention-to-treat. PD-L1=programmed death ligand 1. TPS=tumour proportion score.

reported that pembrolizumab was superior to chemotherapy for overall survival in all PD-L1 TPS populations tested. This trial is registered with ClinicalTrials.gov, NCT02220894.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

3428 patients across all study sites were screened for enrolment (figure 1, appendix). 3019 had samples that were evaluable for PD-L1 expression, of whom 1978 (66%) had a TPS of 1% or greater, including 922 (31%) who had a TPS of 50% or greater. From Dec 19, 2014, to March 6, 2017, 1275 patients were randomly allocated to receive pembrolizumab (n=638) or chemotherapy (n=637). One patient in the pembrolizumab group was randomly assigned treatment after death and, therefore, the intention-to-treat popluation included 1274 patients (637 in each group, figure 1). Important protocol deviations, defined as those that could substantially affect the quality or integrity of key study data or a patient's rights, safety, or wellbeing, were reported in 17 (1%) of 1274 patients (appendix), but only one patient discontinued study treatment because of a study violation (figure 1). The

	Pembrolizumab group (n=637)			Chemotherapy group (n=637)		
	Tumour proportion score ≥50% (n=299)	Tumour proportion score ≥20% (n=413)	Tumour proportion score ≥1% (n=637)	Tumour proportion score ≥50% (n=300)	Tumour proportion score ≥20% (n=405)	Tumour proportion score ≥1% (n=637)
Age (years)	63·0 (56·0–68·0)	63·0 (56·0–69·0)	63·0 (57·0–69·0)	64·0 (57·0–69·0)	64·0 (57·0–69·0)	63·0 (57·0–69·0)
<65	167 (56%)	228 (55%)	359 (56%)	161 (54%)	212 (52%)	348 (55%)
Men	205 (69%)	283 (69%)	450 (71%)	210 (70%)	285 (70%)	452 (71%)
Women	94 (31%)	130 (31%)	187 (29%)	90 (30%)	120 (30%)	185 (29%)
Region of enrolment						
East Asia	92 (31%)	128 (31%)	185 (29%)	94 (31%)	121 (30%)	185 (29%)
Europe	71 (24%)	96 (23%)	149 (23%)	66 (22%)	95 (23%)	137 (22%)
Latin America	53 (18%)	78 (19%)	136 (21%)	63 (21%)	82 (20%)	133 (21%)
Other	83 (28%)	111 (27%)	167 (26%)	77 (26%)	107 (26%)	182 (29%)
ECOG performance status score						
0	96 (32%)	122 (30%)	198 (31%)	91 (30%)	131 (32%)	192 (30%)
1	203 (68%)	291 (70%)	439 (69%)	209 (70%)	274 (68%)	445 (70%)
Smoking status						
Current	57 (19%)	75 (18%)	125 (20%)	59 (20%)	85 (21%)	146 (23%)
Former	178 (60%)	243 (59%)	370 (58%)	174 (58%)	230 (57%)	351 (55%)
Never	64 (21%)	95 (23%)	142 (22%)	67 (22%)	90 (22%)	140 (22%)
Tumour histological features						
Squamous	107 (36%)	148 (36%)	243 (38%)	114 (38%)	156 (39%)	249 (39%)
Non-squamous	192 (64%)	265 (64%)	394 (62%)	186 (62%)	249 (61%)	388 (61%)
Disease status						
Locally advanced	27 (9%)	42 (10%)	76 (12%)	35 (12%)	51 (13%)	84 (13%)
Metastatic	272 (91%)	371 (90%)	561 (88%)	265 (88%)	354 (87%)	553 (87%)
Brain metastases	19 (6%)	23 (6%)	35 (5%)	15 (5%)	22 (5%)	35 (5%)
PD-L1 tumour proportion score						
1–19%	0	0	224 (35%)	0	0	232 (36%)
20–49%	0	114 (28%)	114 (18%)	0	105 (26%)	105 (16%)
≥50%	299 (100%)	299 (72%)	299 (47%)	300 (100%)	300 (74%)	300 (47%)
Previous treatment for non-metastatic disease						
Radiotherapy	40 (13%)	53 (13%)	75 (12%)	39 (13%)	51 (13%)	81 (13%)
Neoadjuvant therapy	1 (<1%)	2 (<1%)	3 (<1%)	5 (2%)	7 (2%)	7 (1%)
Adjuvant therapy	8 (3%)	13 (3%)	18 (3%)	4 (1%)	8 (2%)	12 (2%)

Data are median (IQR) or n (%). Patients in the chemotherapy group received either paclitaxel and carboplatin with or without pemetrexed maintenance or pemetrexed and carboplatin with or without pemetrexed maintenance. ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1.

Table 1: **Baseline characteristics**

patient demographics and disease characteristics were similar between groups and across the TPS populations at baseline (table 1).

At least one dose of study therapy was received by 636 patients in the pembrolizumab group and 615 in the chemotherapy group (figure 1). The chemotherapy regimens administered are summarised in the appendix. Among patients with non-squamous histology in the chemotherapy group, pemetrexed maintenance therapy was received by 196, representing 52% of 375 treated patients, 66% of 296 who completed four cycles of induction therapy, and 74% of 264 treated patients who completed four cycles of induction therapy and for whom pemetrexed maintenance was planned at randomisation.

On Feb 26, 2018, median follow-up was 12·8 months (IQR 6·0–20·0). 87 (14%) of 636 patients who started pembrolizumab were continuing this treatment, and 30 (5%) of 615 treated patients in the chemotherapy group were receiving pemetrexed maintenance therapy (figure 1). At least one subsequent anticancer therapy was received by 240 (38%) of 637 patients in the pembrolizumab group and 282 (44%) of 637 in the chemotherapy group, including 19 (3%) and 126 (20%), respectively, who received subsequent immunotherapy (appendix). After excluding patients still taking pembrolizumab or who had completed or discontinued treatment without later disease progression, 240 (51%) of 474 patients in the pembrolizumab group and 282 (56%) of 504 in the chemotherapy group received subsequent treatment.

356 patients with a PD-L1 TPS of 50% or greater died. Overall survival differed significantly between groups (figure 2). The median survival duration was 20·0 months (95% CI 15·4–24·9) in the pembrolizumab group compared with 12·2 months (10·4–14·2) in the

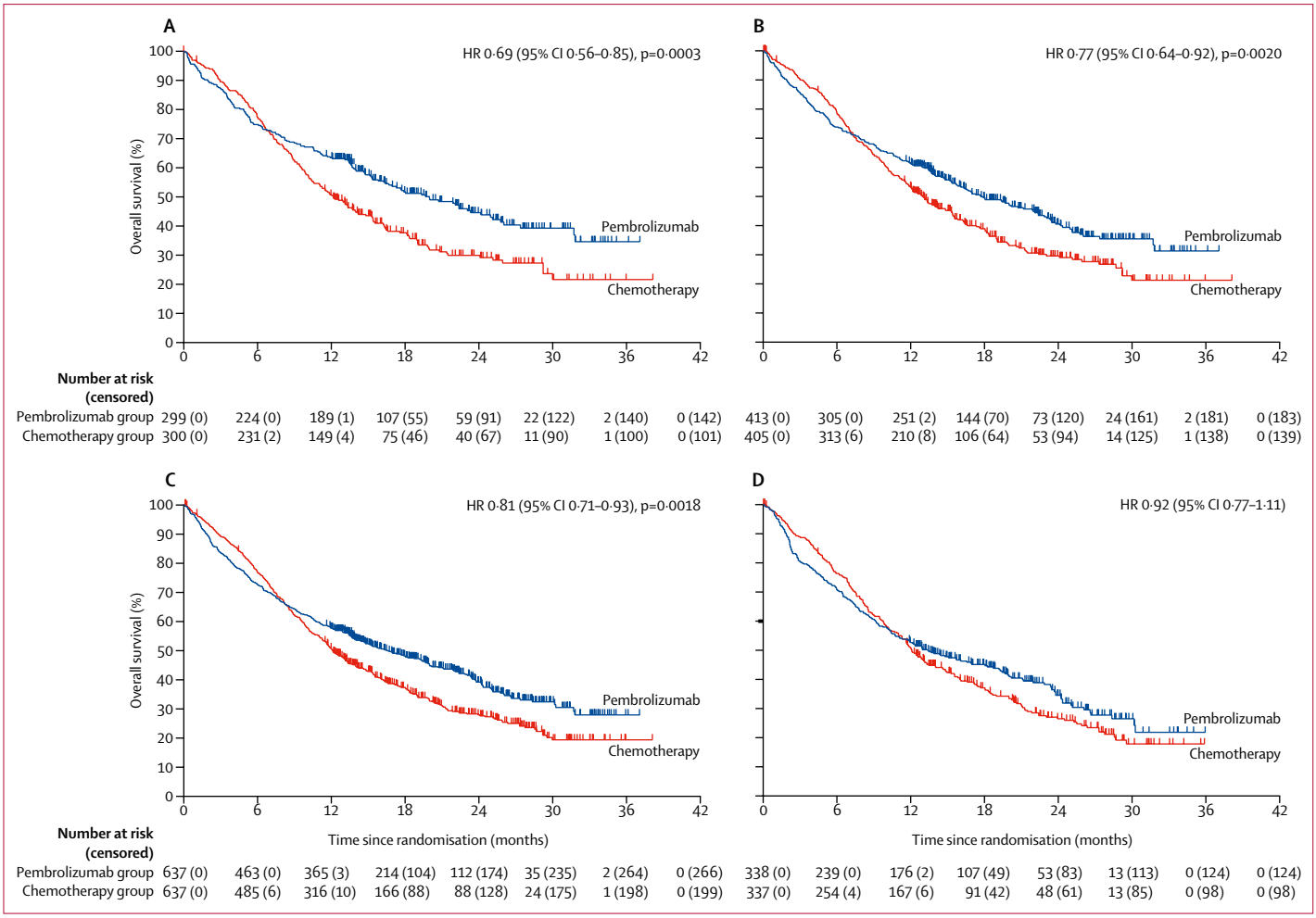

***Figure 2*: Kaplan-Meier estimates of overall survival**

(A) PD-L1 TPS 50% or greater population. (B) PD-L1 TPS 20% or greater population. (C) PD-L1 TPS 1% or greater population. (D) PD-L1 TPS 1–49% population (exploratory analysis). Tick marks indicate censoring of the data at the last time the patient was known to be alive. HR=hazard ratio. PD-L1=programmed death ligand 1. TPS=tumour proportion score.

chemotherapy group. 496 patients in the TPS 20% or greater population died, with the difference in overall survival remaining significant (figure 2). Median survival was 17·7 months (95% CI 15·3–22·1) in the pembrolizumab group compared with 13·0 months (11·6–15·3) in the chemotherapy group. In the TPS 1% or greater population, 809 patients died and overall survival was again significantly different (figure 2). Median survival was 16·7 months (95% CI 13·9–19·7) in the pembrolizumab group compared with 12·1 months (11·3–13·3) in the chemotherapy group. The estimated percentages of patients alive at 24 months in the pembrolizumab and the chemotherapy groups were 45% and 30%, respectively, in the TPS 50% or greater population, 41% and 30% in the TPS 20% or greater population, and 39% and 28% in the TPS 1% or greater population. A survival benefit with pembrolizumab was evident in most subgroups assessed (appendix). For never smokers the HRs were 1·00 or greater, but the 95% CIs overlapped with those of the overall population. In a prespecified, exploratory subgroup analysis, overall survival in the TPS 1–49% population seemed to be similar in the two groups (figure 2). The median survival values were 13·4 months (95% CI 10·7–18·2) in the pembrolizumab group and 12·1 months (11·0–14·0) in the chemotherapy group.

1013 patients died or had disease progression in the PD-L1 TPS 1% or greater population, including 631 in the TPS 20% or greater population and 454 in the TPS 50% or greater population. Median progression-free survival was 7·1 months (95% CI 5·9–9·0) in the pembrolizumab group and 6·4 months (6·1–6·9) in the chemotherapy group in the TPS 50% or greater population, 6·2 months (5·1–7·8) and 6·6 months (6·2–7·3) in the 20% or greater population, and 5·4 months (4·3–6·2) and 6·5 months (6·3–7·0) in the TPS 1% or greater population (figure 3). Significance in the TPS 50% or greater population did not reach the prespecified superiority boundary and, therefore, was not tested in the TPS 20% or greater and 1% or greater populations.

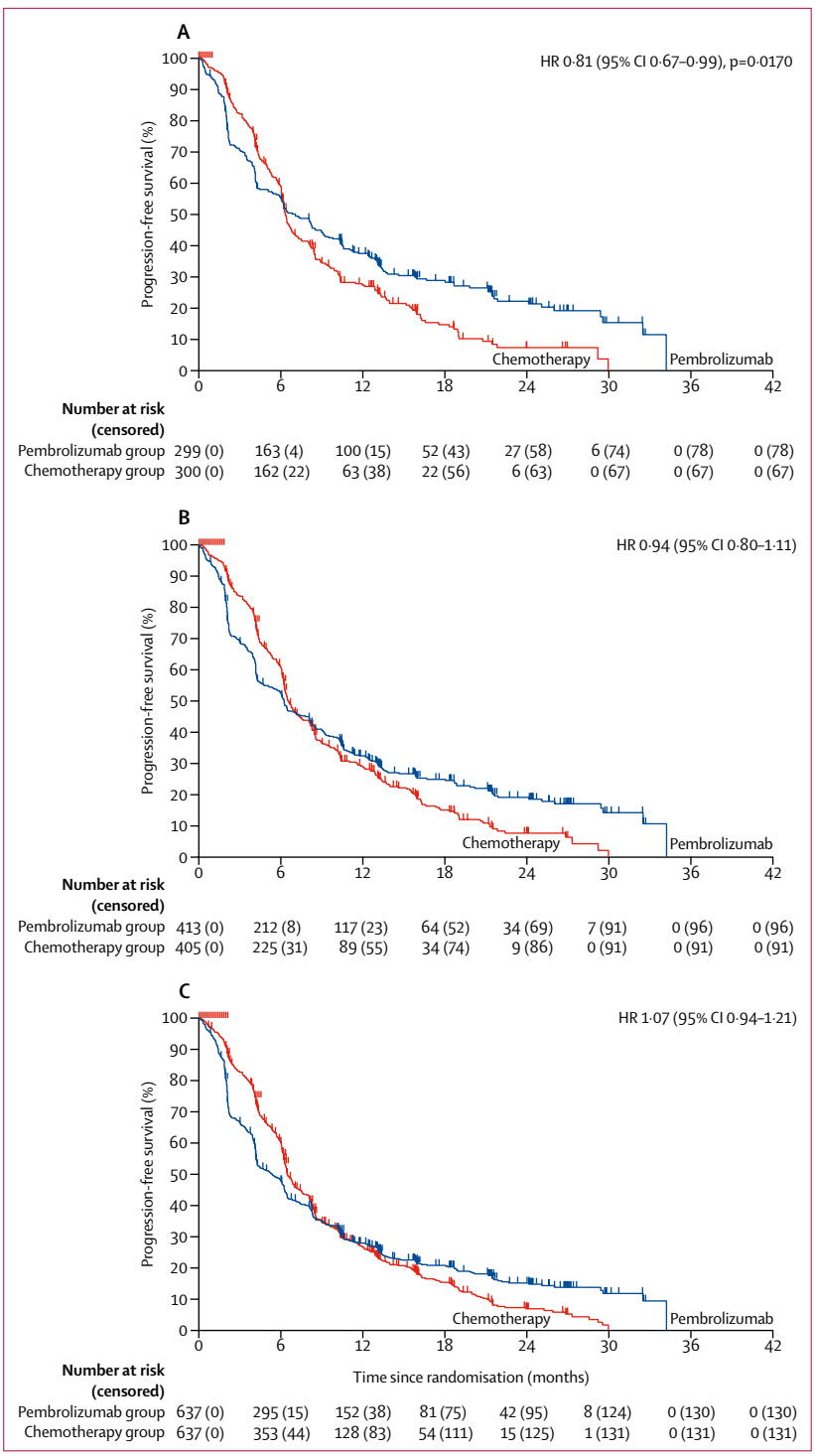

Figure 3: **Kaplan-Meier estimates of progression-free survival**
(A) PD-L1 TPS 50% or greater population. (B) PD-L1 TPS 20% or greater population. (C) PD-L1 TPS 1% or greater population. Significance was not tested for the 20% or greater and 1% or greater populations because the prespecified superiority boundary was not met in the 50% or greater population. Tick marks indicate censoring of the data at the time of the last imaging assessment. HR=hazard ratio. PD-L1=programmed death ligand 1. TPS=tumour proportion score.

In the PD-L1 TPS 50% or greater population, 118 (39%, 95% CI 34–45) of 299 patients in the pembrolizumab group and 96 (32%, 27–38) of 300 patients in the chemotherapy group had an objective response to treatment. The values in the TPS 20% or greater and 1% or greater populations were 138 (33%, 29–38) of 413 versus 117 (29%, 25–34) of 405 and 174 (27%, 24–31) of 637 versus 169 (27%, 23–30) of 637, respectively (appendix). The median duration of response was 20·2 months in the pembrolizumab group in all TPS populations and was 10·8 months, 8·3 months, and 8·3 months, respectively, in the TPS 50% or greater, 20% or greater, and 1% or greater populations in the chemotherapy group (appendix).

In the as-treated population, the median number of doses administered was nine (range one to 36) in the pembrolizumab group and six (one to 42) in the chemotherapy group. Treatment-related adverse events of any grade occurred in 399 (63%) of 636 patients in the pembrolizumab group and 553 (90%) of 615 patients in the chemotherapy group (table 2). Treatment-related adverse events of grade 3 or worse severity occurred in 113 (18%) of 636 patients in the pembrolizumab group and 252 (41%) of 615 patients in the chemotherapy group. Treatment-related adverse events led to death in 13 (2%) and 14 (2%) patients in the pembrolizumab and chemotherapy groups, respectively, and treatment discontinuation in 57 (9%) and 58 (9%), respectively. The most common treatment-related adverse event was hypothyroidism (69 [11%] of 636) in the pembrolizumab group and anaemia (229 [37%] of 615) in the chemotherapy group (table 2, appendix). Treatment-related adverse events of grade 3 or worse severity that occurred in 20 or more patients were pneumonitis in the pembrolizumab group and anaemia, decreased neutrophil count, neutropenia, decreased white blood cell count, and decreased platelet count in the chemotherapy group (table 2, appendix).

Adverse events of interest (events judged likely to be immune mediated and infusion reactions) occurred in 177 (28%) of 636 patients (51 [8%] grade ≥3) in the pembrolizumab group and 44 (7%) of 615 patients (9 [1%] grade ≥3) in the chemotherapy group (table 3). The only grade 3 or worse immune-mediated events that occurred in five or more patients in the pembrolizumab group were pneumonitis, severe skin reactions, and hepatitis (table 3). One patient in the pembrolizumab group died because of pneumonitis that occurred concurrently with disease progression.

Discussion

In this randomised phase 3 study of patients with previously untreated locally advanced or metastatic non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocations, pembrolizumab monotherapy significantly prolonged overall survival compared with standard chemotherapy in patients with a PD-L1 TPS of 50% or greater, 20% or greater, and 1% or greater.

	Pembrolizumab group (n=636)		Chemotherapy group (n=615)	
	Any grade	Grades 3–5	Any grade	Grades 3–5
Any event	399 (63%)	113 (18%)	553 (90%)	252 (41%)
Event leading to discontinuation	57 (9%)	48 (8%)	58 (9%)	43 (7%)
Event leading to death*	13 (2%)	13 (2%)	14 (2%)	14 (2%)
Event occurring in ≥5% of patients in either group†				
Hypothyroidism	69 (11%)	1 (<1%)	2 (<1%)	0
Fatigue	50 (8%)	3 (<1%)	102 (17%)	8 (1%)
Pruritus	46 (7%)	2 (<1%)	15 (2%)	0
Rash	46 (7%)	3 (<1%)	27 (4%)	0
Alanine aminotransferase increased	45 (7%)	9 (1%)	53 (9%)	5 (<1%)
Pneumonitis	43 (7%)	20 (3%)	0	0
Aspartate aminotransferase increased	41 (6%)	4 (<1%)	42 (7%)	2 (<1%)
Decreased appetite	40 (6%)	5 (<1%)	109 (18%)	9 (1%)
Hyperthyroidism	37 (6%)	1 (<1%)	1 (<1%)	0
Anaemia	35 (6%)	4 (<1%)	229 (37%)	80 (13%)
Diarrhoea	34 (5%)	5 (<1%)	46 (7%)	1 (<1%)
Nausea	31 (5%)	0	184 (30%)	7 (1%)
Arthralgia	27 (4%)	0	46 (7%)	0
Asthenia	27 (4%)	3 (<1%)	60 (10%)	10 (2%)
Myalgia	20 (3%)	1 (<1%)	50 (8%)	0
Vomiting	15 (2%)	0	97 (16%)	2 (<1%)
Leucopenia	10 (2%)	0	35 (6%)	10 (2%)
Constipation	8 (1%)	0	68 (11%)	0
Stomatitis	7 (1%)	0	31 (5%)	0
Neutropenia	5 (<1%)	1 (<1%)	88 (14%)	46 (7%)
Peripheral sensory neuropathy	3 (<1%)	0	41 (7%)	6 (1%)
Thrombocytopenia	3 (<1%)	1 (<1%)	56 (9%)	10 (2%)
White blood cell count decreased	3 (<1%)	0	71 (12%)	32 (5%)
Alopecia	2 (<1%)	0	136 (22%)	7 (1%)
Neutrophil count decreased	2 (<1%)	0	86 (14%)	54 (9%)
Platelet count decreased	2 (<1%)	0	64 (10%)	20 (3%)
Neuropathy peripheral	1 (<1%)	0	50 (8%)	5 (<1%)

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. *The adverse events leading to death were cardiac failure acute, death not otherwise specified, encephalopathy, haemoptysis, hypovolaemic shock, ileus, klebsiella infection, malignant neoplasm progression, pneumonitis, pulmonary embolism, respiratory failure, sepsis, and sudden death (all n=1) in the pembrolizumab group, and pneumonia (n=4) and cardiac failure, dyspnoea, infection, ketoacidosis, neutropenic sepsis, pancytopenia, pulmonary embolism, pulmonary sepsis, respiratory distress, and septic shock (all n=1) in the chemotherapy group. †Events are listed in descending order of frequency for any grade of adverse event in the pembrolizumab group.

Table 2: **Treatment-related adverse events in the as-treated population**

	Pembrolizumab group (n=636)		Chemotherapy group (n=615)	
	Any grade	Grades 3–5	Any grade	Grades 3–5
Any event	177 (28%)	51 (8%)	44 (7%)	9 (1%)
Hypothyroidism	77 (12%)	1 (<1%)	9 (1%)	0
Pneumonitis	53 (8%)	22 (3%)	3 (<1%)	1 (<1%)
Hyperthyroidism	39 (6%)	1 (<1%)	4 (<1%)	0
Severe skin reactions	15 (2%)	11 (2%)	2 (<1%)	1 (<1%)
Infusion reactions	10 (2%)	1 (<1%)	26 (4%)	6 (1%)
Thyroiditis	10 (2%)	0	0	0
Hepatitis	9 (1%)	7 (1%)	0	0
Colitis	7 (1%)	4 (<1%)	2 (<1%)	1 (<1%)
Adrenal insufficiency	4 (<1%)	2 (<1%)	1 (<1%)	0
Hypophysitis	3 (<1%)	3 (<1%)	0	0
Nephritis	3 (<1%)	1 (<1%)	0	0
Myocarditis	1 (<1%)	1 (<1%)	0	0
Pancreatitis	1 (<1%)	0	0	0

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The events of interest are infusion reactions and events with an immune-mediated cause regardless of attribution to treatment by investigators. The events are listed in descending order of frequency for any grade of adverse event in the pembrolizumab group. Specific preferred terms and related terms are included.

Table 3: **Adverse events of interest in the as-treated population**

Pembrolizumab also had a better safety profile than chemotherapy.

Consistent with previous studies of pembrolizumab given as monotherapy[8,9] or as part of combination therapy[18] in patients with metastatic non-small-cell lung cancer, there appeared to be a relationship between higher tumour PD-L1 expression and greater efficacy of pembrolizumab. The HR for overall survival was lowest in patients who had a TPS of 50% or greater, which might indicate an increased treatment benefit, but the HR still favoured pembrolizumab in the TPS 1% or greater population. In an exploratory analysis of patients with TPS 1–49%, the 95% CI of the HR for overall survival crossed 1·00. Based on the significant survival benefit observed in the primary TPS 1% or greater population, along with the safety profile compared with chemotherapy, pembrolizumab appears to be a reasonable treatment option for patients with PD-L1-expressing tumours.

The median overall survival seen in the pembrolizumab group in our PD-L1 TPS 50% or greater population is numerically lower than that reported in KEYNOTE-024,[11] although the 95% CIs overlap (20·0 months, 95% CI 15·4–24·9 in KEYNOTE-042 *vs* 30·0 months, 18·3 to not reached in KEYNOTE-024). Of note, these studies enrolled patients in different regions of the world. KEYNOTE-024 was done mainly in North America and western Europe, with only 13% of patients enrolled in east Asia,[10] whereas KEYNOTE-042 was done mainly in Asia-Pacific, eastern Europe, and South America, and enrolled 29% of patients in east Asia. In the KEYNOTE-042 regions there was less availability of and access to therapy,

particularly immunotherapy, which is reflected in the lower percentage of patients in the chemotherapy group who received subsequent immunotherapy (20% *vs* 64% in KEYNOTE-024), although crossover to pembrolizumab was permitted during KEYNOTE-024. Progression-free survival, the primary endpoint of KEYNOTE-024, is less likely to be affected by crossover than overall survival, which was the primary endpoint of KEYNOTE-042 and, thus, why crossover was not permitted KEYNOTE-042. Even after the results of KEYNOTE-024 showed a benefit in patients with a PD-L1 TPS of 50% or greater, we chose not to introduce crossover in KEYNOTE-042. We would have had to limit crossover to patients with a TPS of 50% or greater because benefit had only been shown in this population, and crossover would have been allowed for only part of the trial. Both these factors would have created challenges for study operation and data interpretation. Overall, the use of other subsequent therapies in this study is more representative of real-world clinical practice, where less than half of patients receive second-line or later treatment.[19,20]

Pembrolizumab did not significantly prolong progression-free survival in the PD-L1 TPS 50% or greater population at the time of the second interim analysis, and per the hierarchical statistical analysis plan, the hypotheses of progression-free survival in the TPS 20% or greater and 1% or greater populations were not formally tested. Although significant progression-free survival benefits do not always accompany significant overall survival benefits in studies of immune checkpoint inhibitors,[9,21–24] the absence of this benefit in the TPS 50% or greater population was somewhat unexpected given the significant benefit observed in KEYNOTE-024.[10] PD-L1 expression was assessed with the same assay and in the same central laboratory in both studies, and the distribution of TPS categories across the study populations was similar. The greater heterogeneity of the KEYNOTE-042 patient population in terms of smoking history and availability of susequent therapy might help to explain the discrepant progression-free survival findings. Based on the recommendation of the external monitoring committee, the study is continuing to assess progression-free survival after longer follow-up.

In comparison with pembrolizumab in this study, the PD-1 inhibitor nivolumab did not significantly improve overall survival compared with platinum-doublet chemotherapy in the phase 3 CheckMate 026 study of patients with metastatic or recurrent PD-L1-positive non-small-cell lung cancer.[24] In the primary analysis of CheckMate 026, which included patients with a PD-L1 expression level of 5% or greater, as determined using the 28-8 antibody, median overall survival was 14·4 months (95% CI 11·7–17·4) with nivolumab and 13·2 months (10·7–17·1) with chemotherapy, and the HR was 1·02 (95% CI 0·80–1·30). There was also no overall survival benefit in the exploratory population of patients with a PD-L1 expression level of 50% of greater (HR 0·90, 95% CI 0·63–1·29). When comparing results of KEYNOTE-042 and CheckMate 026, it should be noted that CheckMate 026 permitted crossover after disease progression, whereas KEYNOTE-042 did not. Overall, 60% of patients in the chemotherapy group received subsequent nivolumab, which might have decreased the treatment effect of nivolumab compared with chemotherapy.[13]

Findings from the randomised, double-blind, phase 3 KEYNOTE-189 and KEYNOTE-407 studies[17,25] showed that pembrolizumab in combination with standard-of-care platinum-doublet chemotherapy significantly prolonged overall survival and progression-free survival compared with chemotherapy alone as first-line therapy in patients with metastatic non-squamous and squamous non-small-cell lung cancer, irrespective of PD-L1 TPS. Although pembrolizumab plus chemotherapy might have greater efficacy than pembrolizumab alone in patients with PD-L1-expressing tumours, particularly in those with lower PD-L1 expression levels, a definitive conclusion cannot be made without a prospective direct comparison. Ultimately, the choice of treatment will need to be determined on an individual basis after a discussion between the physician and patient on the risks and benefits of each option and based on patient-specific factors.

The safety profiles for pembrolizumab and chemotherapy in this study were generally consistent with those in previous reports,[8–10] with no new safety signals identified. Despite longer treatment exposure in the pembrolizumab group than in the chemotherapy group, there were fewer treatment-related adverse events of grade 3 or worse. Pneumonitis occurred in 8% of patients, but events of grade 3 or worse severity accounted for less than half of cases (incidence 3%). Importantly, only one patient died because of pneumonitis. This patient had multiple comorbid conditions, including chronic obstructive pulmonary disease and bilateral bronchoalveolar consolidation, as well as disease progression.

A limitation of this study is the open-label design, which probably explains why 22 patients randomised to the chemotherapy group did not receive chemotherapy as assigned. These patients might have received immunotherapy as first-line therapy instead, which could have decreased the benefit of pembrolizumab compared with chemotherapy. Another possible limitation of this study is that only 66% of patients with non-squamous histology in the chemotherapy group received pemetrexed maintenance therapy after completing at least four cycles of platinum-doublet chemotherapy. Despite any concerns regarding suboptimum therapy in patients with non-squamous histology in the chemotherapy group, the results were similar to those previously reported for chemotherapy in non-small-cell lung cancer.[1,26,27]

In conclusion, first-line pembrolizumab monotherapy significantly improved overall survival and was associated with fewer treatment-related adverse events than platinum-based chemotherapy in patients with locally

advanced or metastatic non-small-cell lung cancer without sensitising *EGFR* mutations or *ALK* translocation and whose tumours expressed PD-L1 on at least 1% of cells. The results of KEYNOTE-042, in which overall survival was the primary endpoint, confirm the role of pembrolizumab monotherapy as a standard first-line treatment for non-small-cell lung cancer with high PD-L1 expression and suggest that it is a reasonable treatment option for patients with lower PD-L1 expression levels. The study is continuing to evaluate outcomes after additional follow-up.

Contributors

TSKM, GML, JZ, DK, and GL were involved in the conception, design, and planning of the study. TSKM, Y-LW, I K, DMK, BCC, HZT, GC Jr, VS, KKL, IB, and KK collected the data. JZ did the statistical analysis. All authors interpreted the results. TSKM, GML, JZ, DK, and GL drafted the manuscript, which was critically reviewed, revised, and approved for submission and publication by all authors.

Declaration of interests

TSKM is a member of the board of directors for AstraZeneca, Chi-Med, and Sanomics, has received grants or research support from AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, Merck Sharp & Dohme, Novartis, Pfizer, Roche, SFJ Pharmaceuticals, and XCovery, speakers' fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech, Taiho, and Takeda Oncology, honoraria from ACEA Biosciences, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Fishawack Facilitate, Ignyta, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, OncoGenex Pharmaceuticals, Pfizer, Roche/Genentech, SFJ Pharmaceuticals, Takeda Oncology, and Vertex Pharmaceuticals, is a major stockholder in Sanomics, and is an advisory board member for ACEA Biosciences, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, ChiMed, Cirina, Clovis Oncology, Eli Lilly, Fishawack Facilitate, geneDecode Co, Ignyta, Janssen, Pfizer, Merck Serono, Merck Sharp & Dohme, Novartis, Roche/Genentech, SFJ Pharmaceuticals, Takeda, and Vertex Pharmaceuticals. Y-LW has received honoraria from AstraZeneca, Eli Lilly, Pfizer, Pierre Fabre, Roche, and Sanofi, has had a consulting or advisory role with AstraZeneca, Boehringer Ingelheim, Merck, and Roche, and has received research funding to his institution from Boehringer Ingelheim and Roche. BCC has received honoraria from AstraZeneca, Boehringer Ingelheim, and Roche, has acted as a consultant or adviser for AstraZeneca, Roche and Boehringer Ingelheim, been a member of the speakers' bureau for AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Novartis, and has received research funding from AstraZeneca, Bayer, Novartis, and Yuhan. GC has held consulting or advisory roles for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche, been a member of the speakers' bureau for AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Novartis, and payment for travel, accommodation, and expenses from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche. KK has received research funding from Boehringer Ingelheim, Ono, and Taiho. GML, JZ and DK are employees of Merck Sharp & Dohme. GL has received research funding to the institution from AstraZeneca, EMD Serono, and Merck & Co. The other authors declare no competing interests.

Data sharing

Data will be available according to Merck Sharp & Dohme's data sharing policy, which, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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